HETEROCYCLES, Vol 22, No. 7, 1984

A NOVEL REACTION OF HYDROXYLAMINE WITH SUBSTITUTED 7-AMINO-8-QUINOLINOLS

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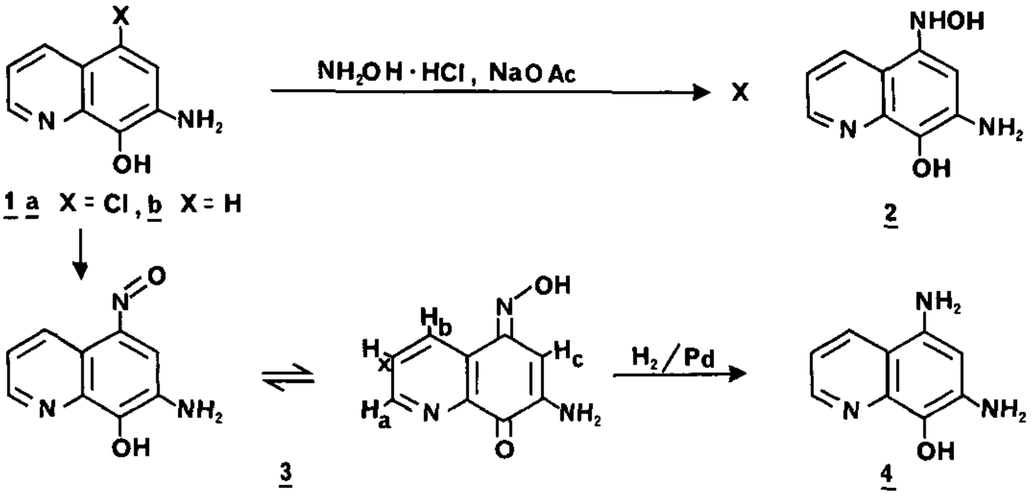
Abstract — A novel reaction of hydroxylamine with substituted 7-amino-8-quinolinols is reported.

When a solution of 7-amino-5-chloro-8-hydroxyquinoline(1a), hydroxylamine hydrochloride (4 eq) and sodium acetate (5 eq) in a 1:1 mixture of DMF and water was heated at 80°C for 18 h under a nitrogen atmosphere, the expected 7-amino-5-hydroxylamino-8-hydroxyquinoline(2) was not obtained. Instead 7-amino-5-nitroso-8-hydroxyquinoline(3) was isolated in 70% yield as an orange solid, mp 210°C with decomposition (Scheme I).

Scheme I



The hygroscopic orange solid was assigned structure 3 on the basis of NMR, IR, and mass spectroscopic evidence as summarized below, and characterization of a chemical derivative.

From elemental analysis and mass spectrum, compound 3 was assigned molecular formula $C_9H_7N_3O_2$. The IR indicated N-O and C=N stretching at 957 cm^{-1} and 1661 cm^{-1} respectively. An intense C=O stretching was seen at 1615 cm^{-1} and no N=O stretching was observed. Similar absorptions are recorded for 4-nitrosophenol which is reported to exist in the quinoid structure[2].

Comparision of the NMR spectrum of 1a and 3 (Table) showed that the chemical shifts were similar in each case except that the Hc singlet of 3 was shifted 0.57 ppm upfield relative to 1a.

Table NMR Spectral Data[†]

Proton[‡]	Compound 1a	Compound 3	Compound 4
Ha	8.72	8.71	8.74
Hb	8.25	8.44	8.21
Hx	7.26	7.57	7.60
Hc	7.36	6.79	5.78

[†] Spectra were observed at 60 and 90 MHz in d$_6$DMSO.

[‡] An ABX splitting pattern could be clearly seen in all three spectra.

Additional proof of structure for compound 3 was provided by characterization of a chemical derivative. Catalytic reduction of 3 gave the known[3-5] 5,7-diamino-8-hydroxyquinoline(4) in 80% yield. This sample was indistinguishable by NMR, IR, and mass spectroscopy from a sample prepared by treating 8-quinolinol with 2.2 eq nitric acid, followed by reduction with sodium dithionite[5].

A search for compound 3 showed that many substituted 8-quinolinols are known[6]. The interest in these compounds stems from their amoebicidal, bactericidal, and fungicidal activities[7]. However, as far as we were able to determine, compound 3 is not reported in the literature.

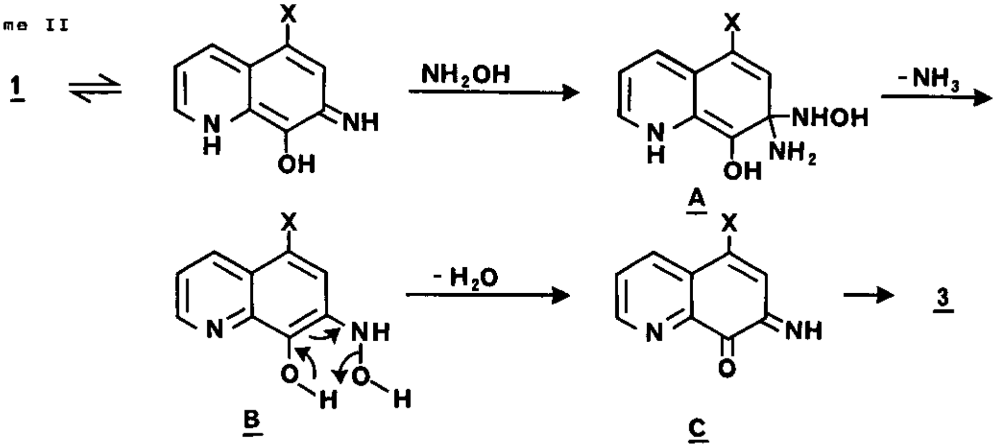
The possible mechanism for the formation of 3 deserves comment. A review of the literature showed that nucleophilic displacement of halogen from haloquiolines can be facile[8]. For example, 2-chloroquinoline[9], 4-chloroquinoline[10], and

4-chloroquinoline-N-oxide[11] react with hydroxylamine hydrochloride to give the respective quinolinyl hydroxylamines.

Therefore, we felt that compound 2 was being produced in the reaction and upon work up, air oxidation converted 2 into 3. Further experiments did not support this hypothesis.

Treatment of either 5-chloro-8-hydroxyquinoline or 2-amino-4-chlorophenol with hydoxylamine hydrochloride and sodium acetate in a 1:1 mixture of DMF and water under a nitrogen atmosphere at 80°C overnight (conditions used in transformation 1a to 3) gave starting material. However, the reaction of 7-amino-8-hydroxyquinoline(1b) under the same conditions produced compound 3. Simple air oxidation upon work up can not account for transformation 1b to 3. These results suggest that intermediates such as A, B and C may be involved in transformation 1 to 3 (Scheme II).

Scheme II



Precedent for the above sequence can be found in two related reactions: 1) the reaction of hydroxylamine with 1-nitronaphthalene to give 1-amino-4-nitronaphthalene[12], and 2) the reaction of hydroxylamine and chloral hydrate with aniline to give isatins[13].

In summary, the new compound 7-amino-5-nitroso-8-quinoline(3) was synthesized by a novel reaction of hydroxylamine with 7-amino-8-quinolinols(1)[14]. Whether intermediate A or another intermediate is involved in the formation of 3 remains to be determined.

REFERENCES

1. Current Address: Wyeth Laboritories, P.O. Box 8299, Philadelphia, PA 19101.

2. W.R. Vaughan and G.K. Finch, J. Org. Chem., 1956, 21, 1201.

3. "Beilstein Handbuch der Organischen Chemie", Verlag von Juluis Springer, Berlin, 1935, XXII, Syst. No. 3423, 503.

4. A. Labert, and D. Magrath, Biochem. J., 1947, 41, 534.

5. T. Urbanski, Roczniki Chem., 1951, 75, 297: Chem. Abstr., 1954, 4546h, 9370i.

6. R. C. Elderfield, "Heterocylic Chemistry", Vol. 4, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 136.

7. R. E. Bambury, "Medicinal Chemistry", Part II, 4th Ed., ed. by M. E. Wolfe, Wiley-Interscience, New York, N. Y., 1979, p. 51.

8. R. K. Smalley, "Heterocyclic Compounds", Vol. 32, ed. by G. Jones, Wiley-Interscience, New York, N. Y., 1977, p. 526.

9. J. Filippi, Bull. Soc. Chim. France, 1968, 1, 259.

10. M. Hamana and K. Funakoshi, Yakugaku Zassi, 1964, 84, 42.

11. E. Ochiai, A. Ohta, and H. Nomura, Chem. Pharm. Bull. Soc. Japan, 1957, 5, 310.

12. C. C. Price and S. T. Voong, Org. Syn., Coll. Vol. III, 1955, 664.

13. A. R. Katritsky and A. J. Boulton, "Advances in Heterocyclic Chemisty", Vol. 18, 1975, ed. by F. D. Popp, Academic Press, New York, N. Y., 1.

14. In the case of transformation 1b to 3, Scheme II would be repeated requiring an extra equivalent of hydroxylamine. Intermediate 8 where X=NHOH would preferentially lose water via a six-member transition state thus explaining the observation that the isomeric 5-amino-7-nitoso-8-hydroxyquinoline is not isolated.

Received, 27th March, 1984